II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 1-25, 32-43, and 68-74 were pending prior to the Office Action dated September 30, 2003. Claims 1, 15-17, and 36 have been amended. Support for the amendments may be found throughout the specification, for example, at page 10, lines 7-10 and page 22, lines 21-25 and in the originally filed claims, such as claim 36. Claims 75-77 have been added. Support for these claims can be found in the specification, for example, at page 56, lines 27-28 and at page 9, lines 9-13, 18-20. No new matter has been added.

The withdrawal of claims 68-74 from consideration is inappropriate. Claim 32 contains the elected species and added claims 68-74 depend from claim 32 and further limit the elected species.

B. Claim Objections

1. Amendment of Claims Due to Election

The Action objects to claims 1, 13, 18-23, and 36-38 because they encompass more than one invention as defined in the restriction requirement (Paper No. 8). The Action contends the claims should be amended so that they read only upon the elected invention. Applicants respectfully traverse this objection.

The MPEP states, "The linking claims must be examined with the invention elected, and should any linking claim be allowed, the restriction requirement must be withdrawn." MPEP 809. Linking claims include "genus claims linking species claims." MPEP 809.03. Claims 1 and 36 are linking claims.

Applicants respectfully request that the examiner provide the authority or citation that requires an applicant to *amend* claims based merely on an election of invention.

2. Recitation of "MDA-7"

The Action objects to claim 1 because of its recitation of "MDA-7" and requires that the abbreviation be spelled out. Claim 1 now recites "Melanoma Differentiation Antigen-7 (MDA-7)."

3. Claims 16 and 17 Are Amended

The Action objected to claims 16 and 17 as being improperly dependent. Claim 16 has been amended to depend from claim 1 instead of claim 13. Similarly, claim 17 has been amended to depend from claim 1 as well.

C. Claims 1-4, 7-25, and 32-43 Are Enabled

The Action rejects claim 1-4, 7-25, and 32-43 under 35 U.S.C. §112, first paragraph, because the specification allegedly does not enable the claimed invention for the following aspects: (1) MDA-7 polypeptide fragments; (2) addition of a secretory signal on an MDA-7 polypeptide; (3) targeting of a nucleic acid to a target site to effect tumor killing. Applicants respectfully traverse this rejection.

1. MDA-7 Fragments Are Enabled

The Action contends that neither the specification, nor art of record, teaches a consensus region that is critical for the function of MDA-7 or the structural correlation of the polypeptide with its function for inhibiting the growth of tumor cells. It also contends that the art of protein chemistry is "one of the most unpredictable areas of biotechnology." It cites the references of Bowie *et al.* as teaching that certain positions in a protein sequence are critical to the three-dimensional structure/function relationship and that these regions can tolerate only conservative substitutions or none at all (page 1306, column 2). The Action also cites the reference of Skolnick *et al.* to support its conclusion that one cannot predictably extrapolate the teaching of the specification to the scope of the claims because the skilled artisan cannot envision the

detailed structure of fragments of SEQ ID NO:2 encompassed by these claims with the function of the fragments. Moreover, it states that determination of the effects of particular modifications and fragmentations are not predictable until they are actually made, citing the reference of Rudinger. For these reasons, the Action concludes that it would have required undue experimentation to practice the invention.

The Action's contention that the specification fails to provide a sufficient teaching for fragments of MDA-7 lacks merit. A closer look at the cited references does not support the Action's conclusion.

For example, the Action's citation to the Skolnick reference is taken out of context with respect to the issue at hand. The Action cites Skolnick for stating 1) "Sequence-based methods for function prediction are inadequate because of the multifunctional nature. However just knowing the structure of the protein is also insufficient for prediction of multiple functional sites" (abstract)"; and 2) "Knowing a protein's three-dimensional structure is insufficient to determine its function." The entire Skolnick paper is focused on the issue of *predicting* what a protein's function *might be* when *only* sequence information is available, such as in the context of genome sequencing-type projects, where cDNA sequences are obtained. This is reflected by the title of the reference, "From genes to protein structure and function: novel applications of computational approaches in the genomic era." The Skolnick reference might be relevant if Applicants were claiming a cDNA sequence for which no utility had been established. However, this reference is not relevant to the claimed invention because a function for MDA-7 is *already* provided and this is recited in the claims.

The Action contends that "Determination of the effects of particular modifications and fragmentations are not predictable until they are actually made and used, hence resulting in a trial

and error situation." Action at page 6. However, the standard for enablement is not the need for "trial and error." The test of enablement is whether the experimentation needed to practice the invention is undue. MPEP § 2164.01 (citing *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916)). In fact, satisfaction of the enablement requirement is not precluded by the necessity of some experimentation. *See Atlas Powder Co. v. E.I. duPont De Nemours & Co.,* 750 F.2d 1569, 1576, 224 U.S.P.Q. 409 (Fed. Cir. 1984). Therefore, even if trial and error were required to practice the invention, the Action has still not met its burden of showing that this is tantamount to requiring "undue experimentation."

The Action relies upon the reference of Rudinger to indicate that "painstaking experimental study" is required to predict the significance of particular amino acids and sequences for different aspects of biological activity. However, this reference is irrelevant to the present invention because it was published in 1976, ***almost 25*** years before the current application was filed. Surely this reference does not reflect the state of the art at the time the application was filed. Particularly notable is the fact that in the last 25 years, recombinant DNA technology has made something that was extremely difficult—requiring perhaps "painstaking experimental study"—25 years ago, such as cloning a gene, a trivial pursuit, as is demonstrated by the completion of the Human Genome Project in the last two years.

In fact, a skilled artisan could readily prepare fragments covered by the claims and test them for function. The specification provides the cDNA sequence for MDA-7 and teaches, for example, that fragments can be generated recombinantly. Specification at pages 35-44.

Applicants respectfully note that the PTO is required, when examining a patent application, to assume that the specification complies with §112 unless it has "acceptable evidence or reasoning" to suggest otherwise. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ

367, 369-370 (CCPA. 1971). Thus, the PTO must provide reasons supported by the record as a whole what the specification is not enabling. *Application of Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219-220 (CCPA 1979). Then and only then does the burden shift to the Applicants to prove that one of ordinary skill in the art could have practiced the claimed invention without undue experimentation. *In re Strahilevitz*, 668 F.2d. 1229, 1232, 212 USPQ 561, 563-64 (CCPA 1982). In this case, the cited references regarding protein sequence and structure do not shift the burden to the Applicants.

Moreover, Applicants provide additional evidence regarding an MDA-7 fragment. The Declaration of Sunil Chada ("Declaration") (Appendix A) indicates that an MDA-7 polypeptide lacking the first 48 amino acids of the full-length sequence induced cell killing in melanoma cells. Declaration at ¶ 6. Moreover, an MDA-7 polypeptide lacking the first 48 amino acids but containing a sequence targeting it to the endoplasmic reticulum suppressed the growth of prostate cancer cells (PC3 cells) and human non-small cell lung carcinoma cells (H1299 cells). Declaration at ¶ 7. Therefore, in view of the foregoing arguments, Applicants respectfully request this ground for the rejection be withdrawn.

2. Secretory Signal with MDA-7 Is Enabled

The Action contends that the reference of Su *et al.* teaches that the tumor suppressing effect of MDA-7 is associated with chromatin remodeling via its nucleus translocation from the cytosol and facilitating the migration of MDA-7 into the nucleus would enhance the selective growth inhibition of malignant but not normal cells. Therefore, the Action contends that the addition of a secretory signal on an MDA-7 polypeptide would prohibit the nucleus translocation and thus abolish the anti-tumor effect of MDA-7.

First, the Su reference cited by the Action does not provide data to indicate that addition of a secretory signal would abolish the anti-tumor effects of MDA-7; it merely speculates in the

Discussion section that facilitating migration of MDA-7 into the nucleus may enhance growth inhibition.

Moreover, the Declaration of Sunil Chada indicates that the first 48 amino acids of the full-length sequence may be cleaved to yield a secreted form of the protein. The present specification indicates that there is a putative secretory signal in the first 46 amino acids of the protein. Specification at page 26, lines 1-9. Furthermore, the Declaration indicates that different forms of MDA-7 were evaluated in prostate cancer cells and human non-small cell lung carcinoma cells. An MDA-7 lacking its own secretion signal but containing a signal targeting it to the endoplasmic reticulum (ER version) showed growth suppression in those cells, as did the full-length MDA-7. However, an MDA-7 targeted to the nucleus or an MDA-7 targeted to the cytoplasm did not. Also, higher levels of apoptosis were observed in cells transfected with full-length and ER versions of MDA-7, compared to the cytoplasmic or nuclear versions of MDA-7.

Therefore, there should not be any issues regarding whether an MDA-7 polypeptide with a signal sequence attached to it can achieve the anti-tumor effect of MDA-7.

3. Administration of MDA-7 Encoding Nucleic Acids Are Enabled

The Action generally contends that while progress has been made in recent years for gene transfer *in vivo*, targeting of naked nucleic acid or any vector to desired cells *in vivo* continues to be unpredictable and inefficient. While difficult to discern clearly, the Action seems to be making three points: 1) gene therapy is unpredictable; 2) targeting of a nucleic acid that is not a viral vector (nonviral vector-nucleic acid) is problematic; and 3) targeting of viral vectors, for example adenovirus, may be problematic.

i) Gene therapy

The Action contends that the gene therapy practitioner, while acknowledging the significant potential of gene therapy for cancer, still recognizes that such therapy was neither

routine nor accepted and await significant development and guidance for its practice. It cites the references of Miller *et al.*, Makrides *et al.*, and Boucher *et al.* to allegedly support its contention.

Once again, a closer examination of the cited references reveals that they do not support the Action's conclusions and also, there is evidence that indicates gene therapy can be practiced according to the specification and knowledge of the skilled artisan.

The Action cites the reference of Miller as saying, "No single delivery system is likely to be universally appropriate, for instance, the requirements of gene therapy for cystic fibrosis are greatly different from those of cancer." Action at page 8, citing page 190 of Miller. By its own admission, the Action renders the next citation to Miller and the citation to Boucher irrelevant because they both involve statements relating to the treatment of cystic fibrosis, while the present invention is related to inhibiting angiogenesis.

As for the reliance on the reference of Makrides, this reference merely states that "the choice of an expression system for production of recombinant proteins depends on many factors...." However, it is not clear how this statement indicates that undue experimentation would be required to practice the invention. Moreover, this reference says nothing about the ability to express MDA-7 or any limitations there might be with its expression.

In fact, there is evidence to support the contention that the claims are enabled. In addition to the data regarding a therapeutic effect from administration of Ad-mda7 in the specification (Examples 1, 4, 6, 9, 10 and 11), there is information relating to the administration of an MDA-7-encoding plasmid in a DOTAP:cholesterol liposome to a nude mouse. In the Declaration of Sunil Chada, he sets forth that nude mice with tumors exhibited reduced tumor growth and reduced levels of CD31 staining after treatment with the DOTAP:Chol-*mda-7*

complex. Declaration at ¶ 9. A reduction in levels of CD31 staining is indicative of reduced vascularization, *i.e.,* inhibition of angiogenesis.

ii) Nonviral-vector nucleic acids

To support its argument that gene therapy using a nonviral vector-nucleic acid, the Action refers to the reference of Deonarain. It cites Deonarain as stating that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time." Action at page 7. The Action also says that the Deonarain reference gives high hope to targeted gene delivery, but that the strategies it discusses are still under investigation and that the reference concludes they were much less efficient than viral gene delivery.

However, there are several reasons the Deonarain reference does not support the broad conclusion that gene therapy with nonviral-vector nucleic acids is unpredictable and inefficient.

The Action's quotation from the first line of the abstract regarding "one of the main obstacles" to fulfilling the promise of gene therapy is taken out of context, because the reference goes on to say that "Viral methods of gene delivery have been studied for a number of years and are effective vectors for gene transfer." The Deonarain reference goes on to say that alternative methods are being explored because of issues relating to mutagenesis, side effects and toxicity—not targeting and expression levels.

Also, the conclusion that the Action cites from the Deonarain reference regarding targeted gene delivery being less efficient than viral gene delivery is followed by the statement, "However, under optimal conditions, enough gene product may be produced to give a therapeutic benefit (*e.g.*, suppress a phenotype of destroy a tumour)." Therefore, the use of the

specific nonviral vector nucleic acid delivery method discussed in the article is not plagued with as many problems as the Action contends.

Furthermore, this reference concerns specifically one type of nonviral vector nucleic acid delivery—"ligand-targeted receptor mediated vectors for gene delivery"—as the title indicates. There are other types of nonviral vector technology, which is not discussed by the Action at all. Therefore, even if one particular type of gene therapy is still undergoing experimentation and improvement, that does not mean that the instant claims reciting a "nucleic acid expressing the human MDA-7 polypeptide in eukaryotic cells" is not enabled.

Moreover, the concern regarding targeting and sustained expression of a gene may be less significant for a gene such as *mda-7*. As the specification indicates, MDA-7 induces apoptosis, and it selectively induces apoptosis in cancer cells, as opposed to normal cells. Specification at page 75. That MDA-7 induces apoptosis in a cell means expression of MDA-7 does not need to be sustained because once it enters the cell and induces apoptosis, that cell is no longer around. Additionally, because MDA-7 selectively induces apoptosis in cancer cells, targeting and sustained expression of MDA-7 are not the issues that they might be for many other gene therapies. Applicants contend that the Action does not raise provide credible reasons supported by the record for its contentions that undue experimentation would be required to practice the invention because it concerns gene therapy with nonviral vector-nucleic acids.

iii) Viral vectors

The Action also contends that it is not clear whether the recited vectors are suitable for the purpose of the instant invention. The Action contends that adenoviral vectors, for example, are known for their tissue tropism of respiratory epithelial cells, which would be a critical limitation for targeting any angiogenesis-dependent cancer.

First, the Action does not cite a reference or provide a declaration or affidavit to support this contention. Furthermore, the literature is replete with example of adenovirus infecting a variety of cell types, in addition to respiratory epithelial cells. In fact, the specification of the instant application shows that adenovirus infected breast cancer cells (Example 4), in addition to lung cancer cells (Example 10). Furthermore, the evidence cited above regarding clinical trials of tumor suppressors provides additional evidence that adenovirus can be used as a gene therapy vector, and that it is not limited to respiratory epithelial cells.

D. Claim 9 is Definite

The Action rejects claim 9 under 35 U.S.C. §112, second paragraph, as being indefinite for its recitation of "pfu." A random search in PubMed for articles published around the time the priority application for this application was filed reveals that "pfu" is used in the literature. Copies of two Journal of Virology papers are provided as examples to show that "pfu" is an appropriate unit dose (See abstracts) (Appendix B).

E. Claims Are Not Anticipated

1. Claims 1-4, 7, 8, 10-15, 24, 25, 35, 36, 42, and 43 Are Not Anticipated by Fisher

The Action rejects claims 1-4, 7, 8, 10-15, 24, 25, 35, 36, 42, and 43 under 35 U.S.C. §102(e) as being anticipated by Fisher (U. S. Patent No. 6, 355,622). Fisher is alleged to teach a method of inhibiting an angiogenesis-dependent cancer in a subject suffering from cancer comprising intratumoral administration of a replication-deficient adenoviral vector encoding the MDA-7 gene (amino acids 1-206 of SEQ ID NO:2) to nude mice bearing human cervical carcinoma cells. The Action contends that Fisher also teaches that the nucleic acid could be imbedded in liposomes introduced into the cell. Finally, it concludes that ectopic expression of MDA-7 inhibits the growth of tumor cells and may provide therapeutic benefit for the treatment

of human cancer, and as such, anticipates the instant claims. Applicants respectfully traverse this rejection.

The Federal Circuit case of *Kalman v. Kimberly-Clark Corp.*, 713 F.2d 760 (Fed. Cir. 1983) states that *identity of invention* is required for anticipation. *Each element* of the claim in issue must be found in a single prior art reference. The claims recite:

> A method of inhibiting angiogenesis in a human patient in need of such treatment comprising administering to the patient an effective amount of a human melanoma differentiation antigen-7 (MDA-7) polypeptide or a nucleic acid expressing the human MDA-7 polypeptide in eukaryotic cells to inhibit angiogenesis.

The Fisher patent, however, does not even mention angiogenesis or inhibition of angiogenesis. Accordingly, it does not anticipate the claimed invention. Applicants respectfully request this rejection be withdrawn.

2. Provisional Rejection Under 35 U.S.C. §102(e) of Claims 1-4, 7-25, and 35-43

The Action provisionally rejects 1-4, 7-25, and 35-43 under 35 U.S.C. §102(e) as being anticipated by copending application number 09/615,154, which has a common inventor with the instant application.

Because this rejection is provisional, Applicants will address this rejection, if necessary, once that application or the current application becomes otherwise allowable.

F. Claims 1, 7-9, 20-23, and 36-41 Are Not Obvious Over Roth *et al.* in View of Fisher

The Action rejects claims 1, 7-9, 20-23, and 36-41 under 35 U.S.C. §103(a) as being unpatentable over Roth *et al.* (U. S. Patent No. 6,069,134) in view of Fisher (U. S. Patent No. 6,355,622). It alleges that Roth teaches a method of administering a DNA damaging agent with an adenoviral vector expressing a tumor suppressor, particularly p53, for the treatment of cancer. The Action further contends that Fisher teaches using adenovirus encoding MDA-7 for the

treatment of cancer and administering vectors to tumor cells, which may provide a therapeutic benefit for the treatment of human cancer in general. The Action acknowledges that Fisher does not discuss the details of such therapy. The Action also argues that claims 20-23 and 37-41 have limitations regarding the timing of the combination therapy that neither of the references discusses. It alleges that these limitations, however, fall within the bounds of optimization for a proper therapeutic regimen that a person of ordinary skill in the art would know. It concludes that thus it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the methods taught by Roth by simply substituting p53 with MDA-7 as taught by Fisher. The ordinary skilled artisan is alleged to have been motivated to modify the claimed invention because the combined therapy would maximize the tumor treating effect of any individual therapy alone. Applicants respectfully traverse this rejection.

Three basic criteria must be met to establish a *prima facie* case of obviousness:

(1) "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings";
(2) "there must be a reasonable expectation of success"; and
(3) "the prior art reference (or references when combined) must teach or suggest all the claim limitations."

MPEP §2142. The present rejection does not meet at least two of these criteria because they do not teach or suggest all of the claim limitations and there was no reasonable expectation of success.

i) Claim limitations not taught by the combination of references

As discussed above, the Fisher patent does not mention angiogenesis. A review of the Roth patent reveals that it too does not mention angiogenesis. The claims recite inhibition of

angiogenesis and consequently, this combination of references does not teach each of the claim limitations.

ii) No reasonable expectation of success

The issue is whether the combination of references provided to the skilled artisan a reasonable expectation of achieving the claimed invention, which is inhibition of angiogenesis by administering a nucleic acid expressing the human MDA-7 polypeptide. As neither reference discusses angiogenesis, the skilled artisan would not have any reason to believe that combining the teachings of the references would provide a way to inhibit angiogenesis in a patient. Accordingly, the skilled artisan had no reasonable expectation of success with respect to the claimed invention. For this reason as well, a proper *prima facie* case is lacking. Applicants respectfully request this rejection be withdrawn.

G. Provisional Double Patenting Rejection

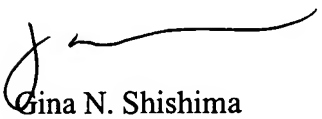
The Action provisionally rejects some of the claims of the application in view of copending U. S. Patent Application No. 09/615,154. Because this rejection is provisional, Applicants will, if necessary, address this rejection once claims in that application or the present application become otherwise allowable.

CONCLUSION

Applicants believe that the foregoing remarks fully respond to all outstanding matters for this application. Applicants respectfully request that the rejections of all claims be withdrawn so they may pass to issuance.

Should the Examiner desire to sustain any of the rejections discussed in relation to this Response, the courtesy of a telephonic conference between the Examiner, the Examiner's supervisor, and the undersigned attorney at 512-536-3081 is respectfully requested.

Respectfully submitted,



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